REMARKS

Claims of Priority under 35 U.S.C. §120

1. According to the Office, applicants are not entitled to the claim priority to U.S. Patent Nos. 7,084,121, 6,770,625 and 6,713,452, for the following reasons.

> Applicant's claim [through amendment (filed 1/6/10) of the specification] for priority that instant application is a continuation-in-part of 10235284 filed 9/5/02 (now US Pat. No. 6770625), and is a continuation application (CON) of 10806523 filed 3/23/04 (now US Pat. No. 7084121) which is a CON of 09873777 filed 6/04/01 (now US Pat. No. 6713452), under 35 U.S.C. 120 is acknowledged.
>
> However, neither 10806523, 09873777 nor 10235284 discloses instant method of treating peripheral pain using a mixture of conjugates comprising the first and second oligomers covalently linked to Lys^{11} and Lys^{18} of salmon calcitonin. Thus, claims 1-3 are not granted priority to 6/04/01 the filing date of 09/342364, nor 3/23/04 the filing of 10806523 nor 9/5/02 the filing date of 10235284. Yet, instant invention is entitled to the filed date 6/24/03 of provisional application 60482130, which has full support for claims 1-3.

The Office further states that the priority documents do not meet the written description requirement. Applicants vigorously disagree.

Initially, it should be noted that a recent decision in the Federal Circuit provide guidance for reviewing the completeness of the specification and that which is already known to the skilled artisan. Notably, the Federal Circuit has addressed this very issue relating to the written description requirement and clarified by the Federal Circuit in *Capon v. Eshhar,* 76 USPQ2d 1078 (Fed. Cir. 2005). Specifically, the *Capon* Court stated that the law must take **cognizance of the scientific facts and the state of scientific knowledge at the time of filing.** More specifically, Judge Newman explained as follows:

> "The 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves **between what is known** and what is added by each inventive contribution." (emphasis added)

Thus, according to the *Capon* Court, **information already known does not have to be disclosed** in the specification to meet the "written description" requirements.

With this in mind, applicants are providing herewith a "Primer" on pain and what is known to skilled artisan regarding bone pain and the type of pain related to Paget's Disease.

Pain is currently classified as being peripheral or central in origin. Peripheral pain originates in muscles, tendons, or in peripheral nerves. Pain originating in the peripheral nerves, such as trauma to nerves, is classified as neurogenic pain. Central pain arises from the central nervous system, such as a primary CNS dysfunction. Another current classification includes nociceptive pain which is pain wherein normal nerves transmit information to the central nervous system about trauma to tissue. Neuropathic pain is pain in which there are structure and/or functional nervous system adaptions secondary to injury that takes place either peripheral or central. The table below provides a brief overview.

TABLE 2.
Mechanistic Characterization of Pain

Any combination may be present in a given individual.

Peripheral (nociceptive)	Neuropathic	Central (non-nociceptive)
» Inflammation or mechanical damage in all tissues » Nonsteroidal antiinflammatory drug (NSAID), opioid responsive » Responds to procedures » Behavioral factors minor » Classic examples: • Osteoarthritis • Rheumatoid arthritis • Cancer pain	» Damage or entrapment of peripheral nerves » Responds to both peripheral (NSAIDs, opioids, sodium channel blockers) and central (tricyclic antidepressants, neuroactive compounds) pharmacological therapy	» Characterized by central disturbance in pain processing (diffuse hyperalgesia) » Tricyclic, neuroactive compounds most effective » Behavioral factors more prominent » Classic examples: • Fibromyalgia • Irritable bowel syndrome • Tension headache • Idiopathic low back pain

Notably, the above table provides a clear distinction regarding the different types of pain including peripheral which is also termed nociceptive and central which in non-nociceptive.

Nociceptive is activity initiated by nociceptors, (also called pain receptors), that can detect mechanical, thermal or chemical changes above a set threshold. Triggering of a nociceptor can result in the experience of pain. Specifically, the stimulation of the nociceptors that innervate bone tissue leads to the sensation of bone pain. Bone tissue is innervated by both myelinated and unmyelinated sensory neurons (A-β, A-δ and C fibers). In combination, they can provide an initial burst of pain (myelinated neurons) followed by a slower and longer lasting dull pain (unmyelinated neurons).

Nociceptors responsible for bone pain can be activated via several mechanisms including deterioration of surrounding tissue, bone destruction, and physical stress which shears the bone, vascular, muscle, and nervous tissue. This type of response is responsible for the bone pain experienced in osteoarthritis, Paget's disease and bone cancer.

The peripheral aspect of bone pain, including that experienced by a subject having Paget's disease is described in numerous articles, such as "Pathophysiology of Bone Pain," June 1, 2001, *Acta Aorthop Scand.*, 72(3) 308-317, a copy attached. In this reference, available to a skilled artisan before the June 4, 2001 priority date of the present invention, it is clear that the peripheral aspects of bone pain relate to nociceptive mechanisms. Mechanical damage such as fractures has been implicated in Paget's disease as described on page 310, column 2, wherein bone pain has been implicated due to the high bone turnover which may cause the microfractures. Further on page 313, column 2, there is a discussion relating to inflammation and it role in bone nociception (peripheral pain) especially in Paget's disease.

Thus, it is very clear that the Office MUST take **cognizance of the scientific facts and the state of scientific knowledge at the time of filing.** More specifically, the Office should recognize that the priority documents do not need to explain every last detail, especially information that is already known to the skilled artisan. **Thus, information already known about peripheral pain relating to bone disease does not have to be disclosed** in the specifications in question to meet the "written description" requirements.

According to 35 U.S.C. §120, applicants may claim benefit to an earlier application if the invention is described to meet the requirements of 112, as shown below:

35 U.S.C. 120 Benefit of earlier filing date in the United States.

An application for patent for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in an application previously filed in the United States, or as provided by section 363 of this title, which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application, if filed before the patenting or abandonment of or termination of proceedings on the first application or on an application similarly entitled to the benefit of the filing date of the first application and if it contains or is amended to contain a specific reference to the earlier filed application.

Further, it is well settled in the law that for a prior application to meet the "written description" requirement with respect to later-filed claims, the prior application need not describe the claimed subject matter in exactly the same terms as used in the claims; it must simply indicate to persons skilled in the art that as of the earlier date the applicant had invented what is now claimed. *Vas-Cath Inc. v. Mahurkar,* 19, USPQ 2d 1111, (Fed. Cir. 1991); see *In re Wertheim*, 191 USPQ 90 (CCPA 1976) (" [L]ack of literal support . . . is not enough . . . to support a rejection under Section 112.") The test is whether the disclosure of the application relied upon reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date. *Ralston Purina Co. v. Far-Mar-Co, Inc* ., 227 USPQ 177 (Fed. Cir. 1985). Clearly, U.S. Patent Nos. 7,084,121, 6,770,625 and 6,713,452, meet these criteria.

Further, it is well settled in the law that a later explicit description of an inherent property, such as treating pain, does not deprive the product or the beneficial method of the filing date of an earlier application. See *Therma-Tru Corp v Peachtree Door Inc.*, 33 USPQ2d 1274 (Fed Cir 1994).

Applicants request reconsideration and a finding that all claims recited in the present application are entitled to the effective filing date of June 4, 2001.

Rejection of Claims and Traversal Thereof

In the April 22, 2010 Office Action,

Claim 3 was rejected under 35, U.S.C.§112, first paragraph;

Claims 1-3 were rejected under 35, U.S.C.§112, second paragraph;

Claims 1-3 were rejected under 35 U.S.C.§102(e) as being anticipated by Soltero et al, (US Patent No. 6,770,625, hereinafter Soltero) as evidenced by Yamamoto et al., (US Patent No. 5,059,587, hereinafter Yamamota) ;

Claim 1was rejected under 35 U.S.C103(a) as being obvious over Lee et al (US Patent No. 6,506,730, hereinafter Lee);

Claim 1 was rejected under 35 U.S.C.§103(a) as being obvious over Russo (US Patent No. 5,976,788, hereinafter Russo) in view of Komarova et al. (*Calcif. Tissue Int.*73, 265-273 (published on line 6/6/2003), hereinafter Komarova) and Lee;

Claim 2 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and in view of Katre, et al (US Patent No. 4,917,888, hereinafter Katre '888) and Lee;

Claim 3 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and Katre, Crotts et al. (US 2003/0017203, hereinafter Crotts), Ekwuribe (US Patent No. 6,638,906, hereinafter Ekwuribe) and Lee; and

Claims 1-2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 15, 70 and 72 of US Patent No. 6,713,452.

Applicants traverse these rejections and insist that none of the cited references alone or in combination defeats the patentability of the presently claimed invention.

Rejection under 35 U.S.C.§112, first paragraph

Claim 3 was rejected under 35, U.S.C.§112, first paragraph as failing to comply with the written description requirement. Applicants have amended claim 3, thereby obviating this rejection and request the withdrawal of same.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1 and 3 were rejected under 35, U.S.C.§112, second paragraph as being indefinite for failing to particularly point and out and distinctly claim the subject matter which applicant regards as the invention. Applicants have amended claims 1 and 3, thereby obviating this rejection and request the withdrawal of same.

Rejection under 35 U.S.C.§102(e)

Claims 1-3 were rejected under 35 U.S.C.§102(e) as being anticipated by Soltero with a filing date of September 5, 2002. Applicants insist that they are entitled to the priority date of June 4, 2001 thereby rendering this reference as non-anticipatory. Thus, this reference is no longer competent prior art and the rejection should be withdrawn.

Rejections under 35 U.S.C.§ 103(a)

1. Claim 1 was rejected under 35 U.S.C103(a) as being obvious over Lee. Applicants insist that Lee does not disclose, teach or suggest the presently claimed invention.

Applicants' invention, as set forth in claim 1, describes a method for **orally administrating** to the subject an effective amount of a **substantially monodispersed mixture of conjugates**, wherein the conjugate comprises a first oligomer and a second oligomer **conjugated at the Lys^{11} and Lys^{18} amine functionality of calcitonin.**

According to the Office, Example 4 of the Lee reference shows the production of a diconjugate wherein pegylation occurs at Lys^{11} and Lys^{18} of calcitonin. Applicants submit that Example 4 does not teach a diconjugate with a PEG at both Lys^{11} and Lys^{18} functionality but instead Example 4 only teaches monconjugates. Example 4 refers to placement of PEG moieties at different pHs and this is discussed in the Brief Description of the Figures and shown in Figure 2, as recreated below.

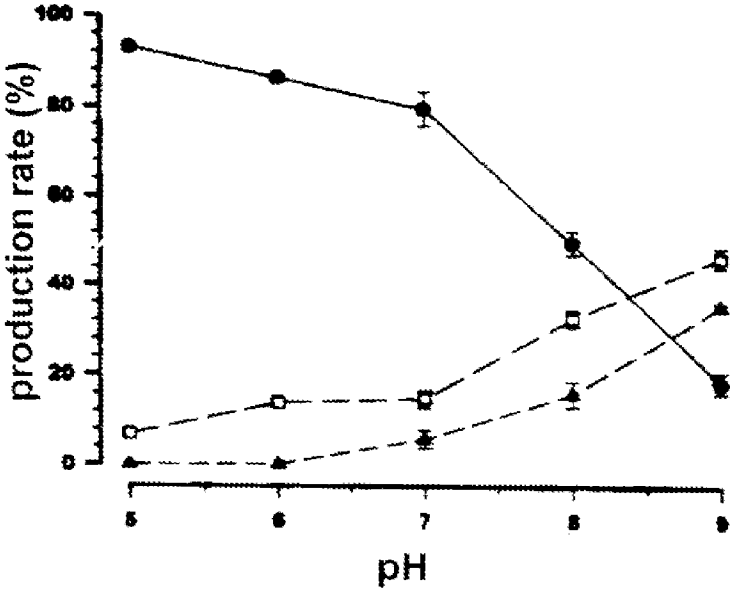
FIG. 2 shows the pH effect on the production of mono-PEG-sCT when PEG is conjugated with N-terminus of calcitonin, Lys^{18} or Lys^{11}, where

●; mono-PEG-sCT(N-terminal conjugate),

□; mono-PEG-sCT(Lys^{18}-conjugate),

▲; mono-PEG-sCT(Lys^{11})-conjugate).

FIG. 2



It is evident as stated in Example 4 that as the pH increases to 8 or above more monoconjugated calcitonin at the Lys^{11} and Lys^{18} amine functionalities is produced, albeit individually. There is nothing in this example that discusses, teaches or suggests a calcitonin conjugate with a PEG moiety at two lysine amine groups at the same time. Thus, this Lee reference does not teach or suggest each of the recited limitations of the presently claimed invention.

Further, the Lee reference only describes compositions for nasal administration. Thus, the Lee reference does not teach or suggest the presently claimed invention, but instead teaches away from going in the direction of applicants' claimed invention. Specifically one skilled in the art reading Lee would quickly note that Lee is teaching away from any orally administered compounds.

The Office has stated numerous times that because injection causes pain that there is a need to develop other routes which is exactly what Lee accomplished. However, one reading this Lee reference would quickly note that Lee discourages the use of oral route, and as such, would never consider going in the oral direction just because an injection is painful. Lee immediately discussed the negative side effects of oral administration and instead went in the direction of nasal delivery. For example, at the bottom of column 1, Lee discusses the disadvantages of oral compounds, as recreated below:

> In fact, the nasal mucosa is a direct absorption route through which drugs can circumvent the liver metabolism, which is a great hindrance to the utilization of drugs in the body upon oral administration. Thus, the nasal transmucosal route has an advantage over the oral route in that the body utilization of drugs can be significantly improved.

Further, Lee reiterates the negative side of oral administration at the bottom of column 3 and recreated below:

> As mentioned above, the nasal transmucosal delivery of peptides alone is significantly improved in absorption efficiency compared with the oral administration because the peptides are not subjected to liver metabolism, but poor in the bioavailability of the peptides because they are degraded by endogenous enzymes.

It is well settled in the law that if a cited reference teaches away from going in the direction of applicants' claimed invention then the Office has not established a *prima facie* case of obviousness. For example, Lee has expressly stated that orally administration of compositions is unacceptable because of the results that occur to the compound in the liver. According to the ruling in *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984), if the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. This concept is further addressed in the MPEP, wherein section § 2143.01 V – VI states that:

> "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."

Thus, even though the Office seems to be speculating that Lee does not discourage the use of oral route, the specification of Lee expressly states the direct opposite and does discourage a skilled artisan from using an oral route. Thus, the Office has not established a *prima facie* case of obviousness and this rejection must be withdrawn.

2. Claim 1 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and Lee. Applicants insist that this proposed combination does not in any way teach and/or suggest the presently claimed invention.

Initially, it should be noted that the present invention has an effective filing date of June 4, 2001 and the Komarova reference was not published until June 6, 2003. As such, this Komarova reference is not competent prior art and must be removed from this rejection.

The Office has already admitted that the Russo reference does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT. Further as stated, above, Lee does not teach or suggest PEGylation at Lys^{11} and Lys^{18} residues of CT and clearly teaches away from oral administration.

As the proposed combination does not teach or suggest each and every element of claim 1, applicants request the withdrawal of this rejection for obviousness.

3. Claim 2 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova and in view of Katre and Lee. Applicants insist that the proposed combination suffers from the same shortcomings as that of the obviousness rejection of claim 1.

As previously stated Komarova is not competent prior art and must be removed. Russo does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT. Further as stated, above, Lee does not teach or suggest PEGylation at Lys^{11} and Lys^{18} residues of CT and clearly teaches away from oral administration. The addition of Katre does not overcome the shortcomings of the three references because even with all combined disclosures, the presently claimed invention is not disclosed, taught or suggested. As the proposed combination does

not teach or suggest each and every element of claim 2, applicants request the withdrawal of this rejection for obviousness.

4. Claim 3 was rejected under 35 U.S.C.§103(a) as being obvious over Russo in view of Komarova, Katre, Crotts, Ekwuribe and Lee. Applicants insist that the proposed combination suffers from the same shortcomings as that of the obviousness rejections of claims 1 and 2.

As previously stated Komarova is not competent prior art and must be removed. The Office has already admitted that the Russo reference does not teach use of PEGylated CT for treating pain, wherein the PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT. Lee does not teach or suggest PEGylation at Lys^{11} and Lys^{18} residues of CT and clearly teaches away from oral administration. The addition of Katre or Crotts does not overcome the shortcomings of the Komarova, Russo and Lee references because the presently claimed invention is not disclosed, taught or suggested. As the proposed combination does not teach or suggest each and every element of claim 3, applicants request the withdrawal of this rejection for obviousness.

In light of the above discussion and the fact that each and every recited limitation of applicants' claimed invention is not disclosed or suggested in the cited references, applicants submit that the Office has not met its burden of establishing a *prima facie* case of obviousness. Accordingly, applicants respectfully request that all the above rejections of the pending claims, based on obviousness, be withdrawn.

Obviousness-Type Double Patenting

Claims 1-2 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8, 15, 70 and 72 of US Patent No. 6,713,452. Applicants will file a Terminal Disclaimer when all other issues relating to patentability have been withdrawn.

Petition for Extension and Fees Payable

Applicants petition for a three (3) month extension and the fee for such extension is being paid herewith by electronic transfer. If any additional fee is found due for entry of this amendment, the Commissioner is authorized to charge such fee to Deposit Account No. 13-4365 of Moore & Van Allen.

Conclusion

Applicants have satisfied the requirements for patentability. All pending claims are free of the art and fully comply with the requirements of 35 U.S.C. §112. It therefore is requested that Examiner Liu, reconsider the patentability of all pending claims, in light of the distinguishing remarks herein and withdraw all rejections, thereby placing the application in condition for allowance. Notice of the same is earnestly solicited. In the event that any issues remain, Examiner Liu is requested to contact the undersigned attorney at (919) 286-8089 to resolve same.

Respectfully submitted,

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